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Phase: I
Title: A Phase I Safety Study in Patients with Severe Hemophilia B (Factor IX Deficiency) Using Adeno-Associated Viral Vector to Deliver the Gene for Human Factor IX into the Liver.
Principal Investigator: Bertil Glader, MD, PhD, Stanford University, 650-723-5535 or bglader@leland.stanford.edu
Disease: Inherited X-Linked Recessive// Hemophilia B
Vector: Adeno-Associated Virus
Route of Administration: Intrahepatic Artery Injection
Gene: Factor IX Gene Elibility/Exclusion
Criteria: Open to individuals 18 years of age or older with severe hemophilia B. Subjects with a known history of allergic reaction to X-ray dye may not participate.
Status: Ongoing

Scientific Abstract

Hemophilia B is the bleeding diathesis that results from a deficiency of blood coagulation factor IX. The disease is X-linked and affects approximately 1 in 30,000 males. Most individuals with hemophilia B have severe disease, with factor IX levels of <1% of normal. The major morbidity is arthropathy from recurrent spontaneous joint bleeds; the major morbidity (and most common cause of premature death before the AIDS era) is central nervous system hemorrhage. The prevalence of CNS bleeding ranges from 2.6 and 13.8% with mortality rates between 20 and 50% and morbidity rates (seizures, motor impairment or mental retardation) of 40-50% in survivors. These bleeds occur predominantly in patients with severe disease (<1% factor level), thus, supporting the concept that raising the levels of factor even slightly would improve the chances to avoid this life-threatening complication of the disease. The incidence of arthropathy and of CNS hemorrhage can be reduced by the use of prophylactic regimens, the goal of which are to maintain trough factor levels >1% of normal. Since there is direct correlation of the severity of the disease with the level of factor IX, analyses of hemostatic parameters (particularly, whole blood clotting time and activated partial thromboplastin time) and of human factor IX (by ELISA) provide readily quantifiable measurements of treatment efficacy.

Recombinant AAV vectors show great promise for therapeutic success in the treatment of hemophilia and certain genetic diseases when delivered to the liver. The exact mechanism(s) involved in transduction is not known. There is strong evidence that at least a portion of the proviral genomes are integrated in head to tail concatemers. Episomal non-integrated, transciptionally active concatemers also are likely to exist. In mice, the vector genomes appear to enter almost every hepatocyte after intraportal administration but only about 5% of the hepatocytes become stably transduced over a period of about 5 to 6 weeks. In mice, curative levels of factor IX have been achieved while in dogs, therapeutic levels of about 1-2% of the normal level of factor IX have been accomplished with relatively small doses compared to the rodent studies.

The overall purpose of this research is to determine the safety of hepatic artery injection of an AAV vector expressing human factor IX into patients with severe hemophilia B. 1) Evaluate the safety of inter-patient dose escalations of an adenoassociated virus (AAV) vector containing the gene for human factor IX (AAV-hFIX) administered into the hepatic artery. Toxicity related to the delivery of AAV-hFIX will be evaluated locally and systemically. 2) Determine whether inhibitory antibodies against factor IX develop in patients receiving AAV-hFIX by hepatic artery administration. 3) Determine whether gene transfer is affected by the presence of preexisting antibodies against AAV. 4) Determine duration of expression of an AAV vector delivered to the liver in humans. 5) Determine whether therapy with AAV vector results in transfer to human germline cells. 6) Evaluate potential efficacy by measuring presence and activity of the transgene product. Analyses will be done to detect the presence of protein expression in blood by measurement of hemostatic parameters and factor IX antigen by ELISA.

Non-technical Abstract

Hemophilia B is the bleeding diathesis that results from a deficiency of blood coagulation factor IX. The disease is X-linked and affects approximately 1 in 30,000 males. Most individuals with hemophilia B have severe disease, with factor IX levels of <1% of normal. The major morbidity is arthropathy from recurrent spontaneous joint bleeds; the major morbidity (and most common cause of premature death before the AIDS era) is central nervous system hemorrhage. The prevalence of CNS bleeding ranges from 2.6 and 13.8% with mortality rates between 20 and 50% and morbidity rates (seizures, motor impairment or mental retardation) of 40-50% in survivors. These bleeds occur predominantly in patients with severe disease (<1% factor level), thus, supporting the concept that raising the levels of factor even slightly would improve the chances to avoid this life-threatening complication of the disease. The incidence of arthropathy and of CNS hemorrhage can be reduced by the use of prophylactic regimens, the goal of which are to maintain trough factor levels >1% of normal. Since there is direct correlation of the severity of the disease with the level of factor IX, analyses of hemostatic parameters (particularly, whole blood clotting time and activated partial thromboplastin time) and of human factor IX (by ELISA) provide readily quantifiable measurements of treatment efficacy.

Recombinant AAV vectors have been shown to result in safe and efficacious gene transfer when administered into the liver of animals that suffer from hemophilia B. The overall purpose of this research is to determine the safety of hepatic artery injection of an AAV vector expressing human factor IX into patients with severe hemophilia B. 1) Evaluate the safety of inter-patient dose escalations of an adeno-associated virus (AAV) vector containing the gene for human factor IX (AAV-hFIX) administered into the hepatic artery. Toxicity related to the delivery of AAV-hFIX will be evaluated locally and systemically. 2) Determine whether inhibitory antibodies against factor IX develop in patients receiving AAV-hFIX by hepatic artery administration. 3) Determine whether gene transfer. is affected by the presence of pre-existing antibodies against AAV. 4) Determine duration of expression of an AAV vector delivered to the liver in humans. 5) Determine whether therapy with AAV vector results in transfer to human germline cells. 6) Evaluate potential efficacy by measuring presence and activity of the transgene product. Analyses will be done to detect the presence of protein expression in blood by measurement of hemostatic parameters and factor IX antigen by ELISA.

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